Access DB# _____

SEARCH REQUEST FORM
(STIC)

Requestor's Name: David Lukton Examiner number: 71263 Date: 8-15-05

Art Unit: 1654 Phone number: 571-272-0952 Serial Number: 10-719599

Mail Box: 3-C-70 Examiner Rm: 3-B-75 Results format: paper

* * * * * * * * * * * *

Title: Neuroprotective Agents

Applicants: SUNDSTROM, LARS ERIC; IANNOTTI, FAUSTO; BRADLEY, MARK; PRINGLE, ASHLEY KER

Earliest Priority Date: 12/16/97

* * * * * * * * * * * *

Applicants are claiming the compounds on the attached sheet.

R^2 = hydrogen or alkyl or acyl or R-NHCO- (R = alkyl or aryl);

R^3 = hydrogen or alkyl or acyl or R-NHCO- (R = alkyl or aryl);

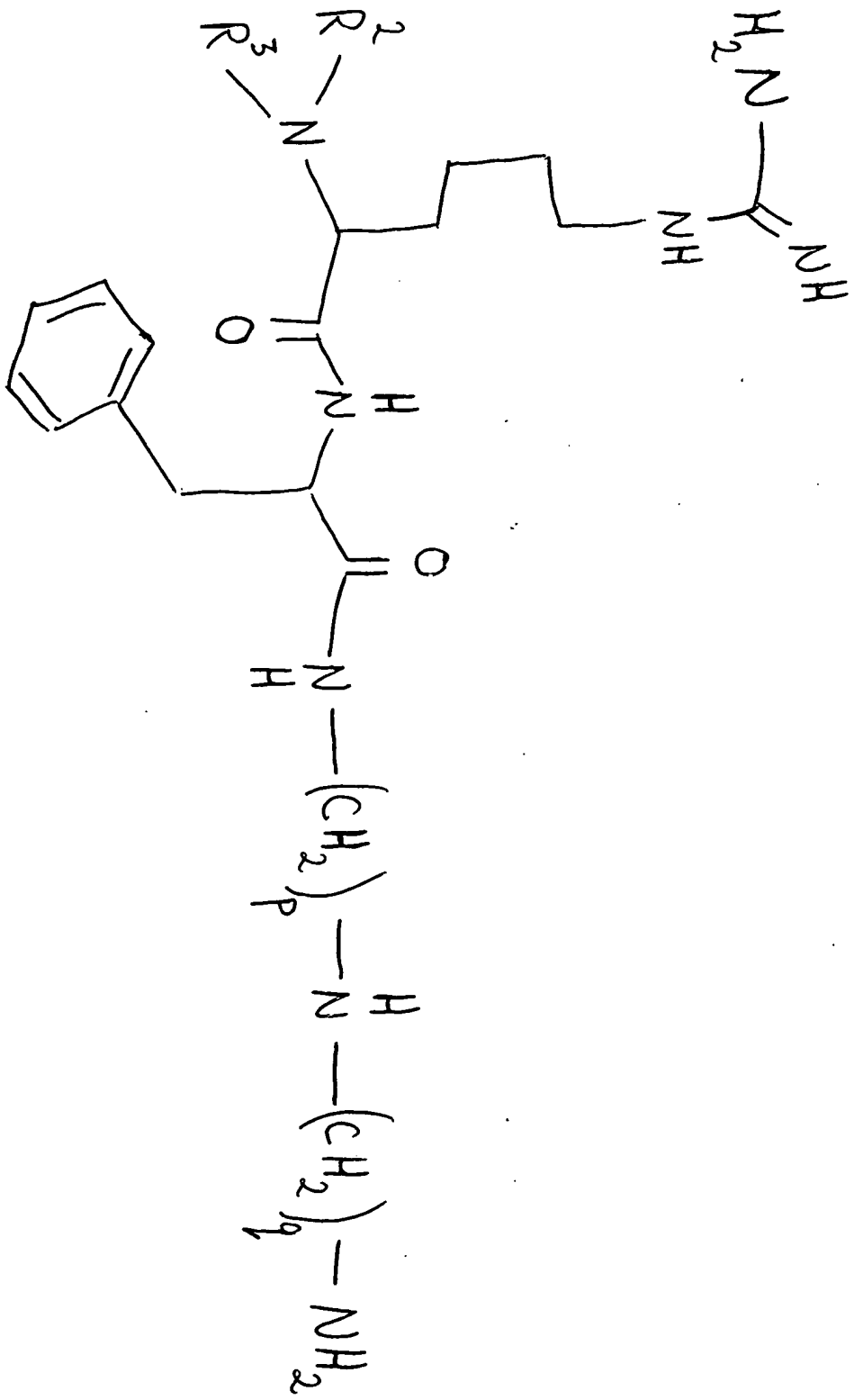
p = an integer of 3 or 4;

q = an integer of 3 or 4

STAFF USE ONLY Type of Search Vendors and cost where applicable

Searcher: _____ NA Sequence (#)_____ STN _____

10/719599



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L2           0 SEA SSS SAM L1
L3           1 SEA SSS FUL L1
L4             STR L1
L5           0 SEA SSS SAM L4
L6           1 SEA SSS FUL L4
L7           1 SEA ABB=ON  L3 OR L6

     FILE 'HCAPLUS' ENTERED AT 11:23:05 ON 12 MAY 2004
L8           2 SEA ABB=ON  L7

     FILE 'CAOLD' ENTERED AT 11:23:33 ON 12 MAY 2004
L9           0 SEA ABB=ON  L7

     FILE 'HCAPLUS' ENTERED AT 11:23:42 ON 12 MAY 2004
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               SELECT RN L8 1-2

     FILE 'REGISTRY' ENTERED AT 11:24:58 ON 12 MAY 2004
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               191277-14-2/BI OR 227758-28-3/BI OR 227758-32-9/BI OR 227758-33
               -0/BI OR 227758-34-1/BI OR 227758-35-2/BI OR 227758-36-3/BI OR
               227758-37-4/BI OR 11062-77-4/BI OR 19059-14-4/BI OR 191277-15-3
               /BI OR 222640-12-2/BI OR 227758-27-2/BI OR 227758-29-4/BI OR
               227758-30-7/BI OR 227758-31-8/BI OR 227758-40-9/BI OR 227758-41
               -0/BI OR 227767-50-2/BI OR 446882-39-9/BI OR 577692-72-9/BI)

     FILE 'HCAPLUS' ENTERED AT 11:36:35 ON 12 MAY 2004
L11          2 SEA ABB=ON  L8 AND L10
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1 compd. from Reg. - all done at ot, attached

2 cits from CA Plus — inventors

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L4                STR
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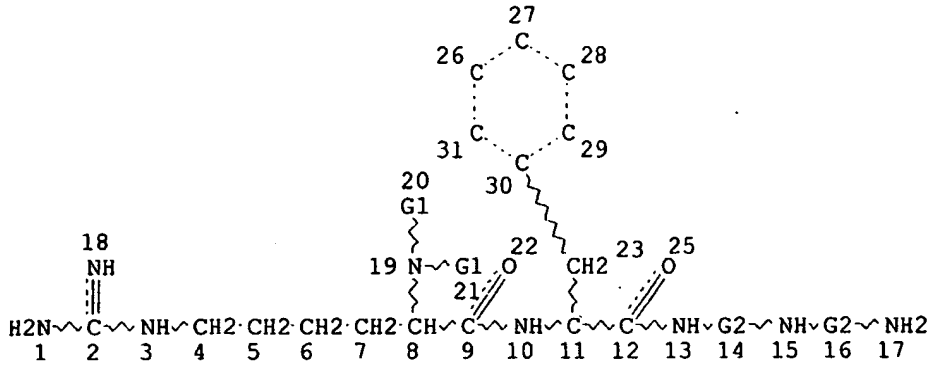


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VAR G1=H/C/O
REP G2=(3-4) CH2
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE
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L6              1 SEA FILE=REGISTRY SSS FUL L4
L7              1 SEA FILE=REGISTRY ABB=ON  L5 OR L6
L8              2 SEA FILE=HCAPLUS ABB=ON  L7
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                  577692-72-9/BI)
L11             2 SEA FILE=HCAPLUS ABB=ON  L8 AND L10
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L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:633453 HCAPLUS
DOCUMENT NUMBER: 139:159957
TITLE: Spermidine derivatives for the treatment of chronic neurodegenerative diseases
INVENTOR(S): Morrison, Barclay, III; Pringle, Ashley Ker; Sundstrom, Lars Eric; Wulfert, Ernst
PATENT ASSIGNEE(S): University of Southampton, UK
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066037	A1	20030814	WO 2003-GB507	20030205

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-2645 A 20020205
OTHER SOURCE(S): MARPAT 139:159957
AB Spermidine derivs. are provided that are useful in treating chronic neurodegenerative diseases or conditions in mammals, e.g. Alzheimer's disease, Parkinson's disease, Huntington's chorea and multiple sclerosis.
IT **11062-77-4**, Superoxide **19059-14-4**, Peroxynitrite
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(spermidine derivs. for treatment of chronic neurodegenerative diseases)
RN 11062-77-4 HCAPLUS
CN Superoxide (8CI, 9CI) (CA INDEX NAME)

O=O

RN 19059-14-4 HCAPLUS
CN Peroxynitrite (8CI, 9CI) (CA INDEX NAME)

O=N-O-O⁻

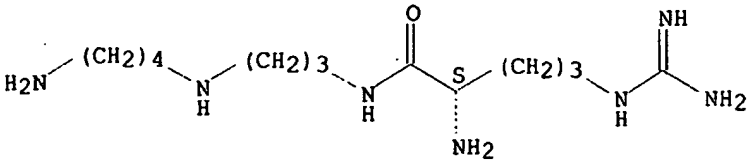
IT **577692-72-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(spermidine derivs. for treatment of chronic neurodegenerative diseases)

RN 577692-72-9 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

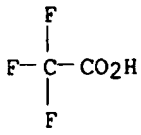
CRN 191277-14-2
CMF C13 H31 N7 O

Absolute stereochemistry.



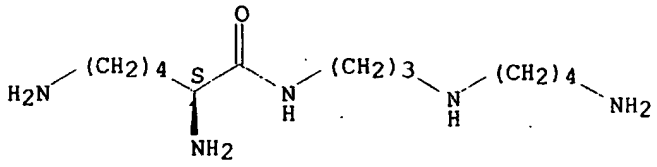
CM 2

CRN 76-05-1
CMF C2 H F3 O2



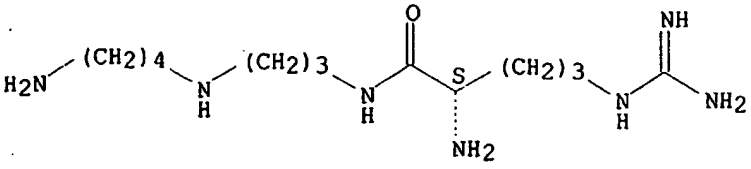
IT **134951-15-8 191277-14-2 227758-28-3**
227758-30-7 227758-32-9 227758-33-0
227758-34-1 227758-35-2 227758-36-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(spermidine derivs. for treatment of chronic neurodegenerative diseases)
RN 134951-15-8 HCAPLUS
CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



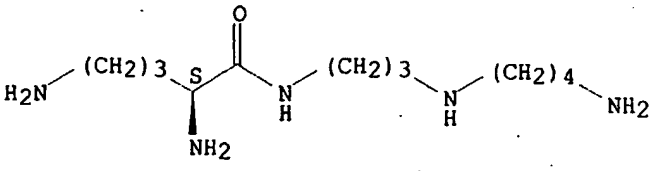
RN 191277-14-2 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



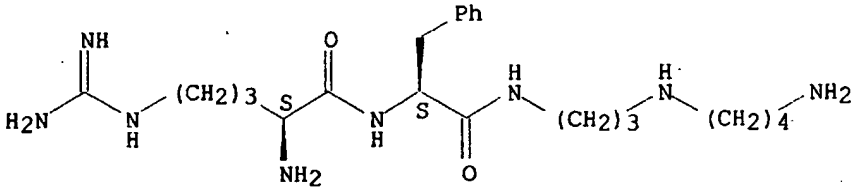
RN 227758-28-3 HCAPLUS
CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



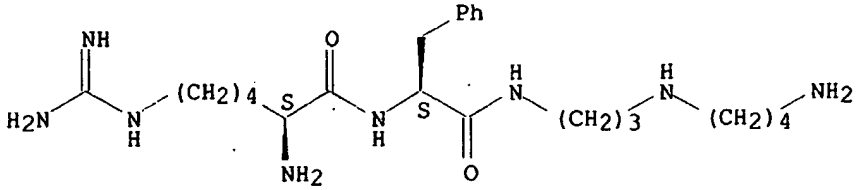
RN 227758-30-7 HCAPLUS
CN L-Phenylalaninamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



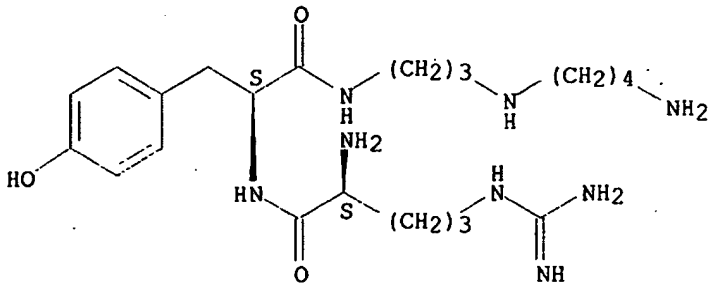
RN 227758-32-9 HCAPLUS
CN L-Phenylalaninamide, N6-(aminoiminomethyl)-L-lysyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



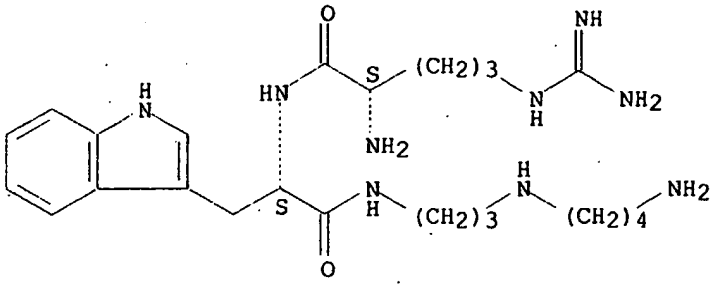
RN 227758-33-0 HCAPLUS
CN L-Tyrosinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



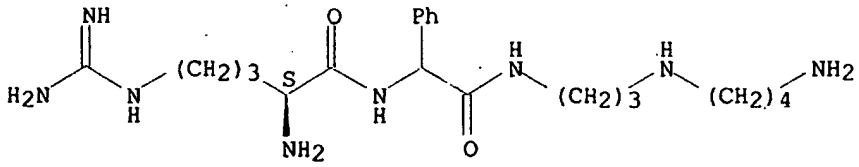
RN 227758-34-1 HCAPLUS
CN L-Tryptophanamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



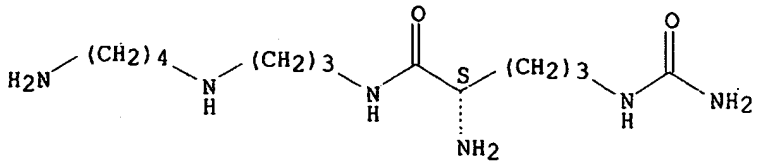
RN 227758-35-2 HCAPLUS
CN Glycinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



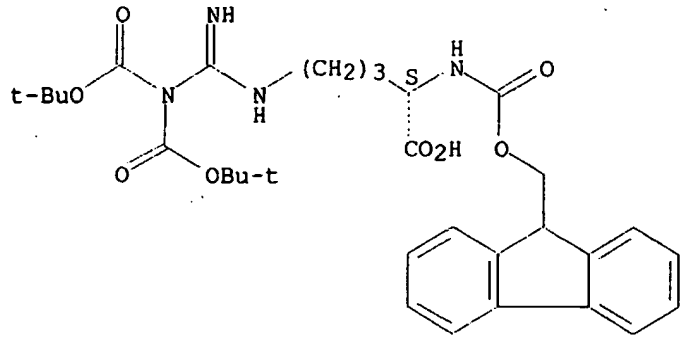
RN 227758-36-3 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

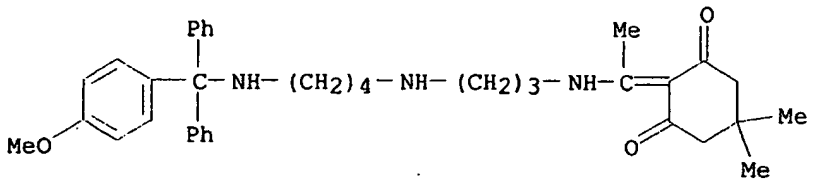


IT **222640-12-2 446882-39-9D**, resin-bonded
RL: RCT (Reactant); RACT (Reactant or reagent)
(spermidine derivs. for treatment of chronic neurodegenerative diseases)
RN 222640-12-2 HCAPLUS
CN 2-Oxa-4,9,11-triazadodecan-12-oic acid, 5-carboxy-11-[(1,1-dimethylethoxy)carbonyl]-1-(9H-fluoren-9-yl)-10-imino-3-oxo-, 12-(1,1-dimethylethyl) ester, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 446882-39-9 HCAPLUS
CN 1,3-Cyclohexanedione, 2-[1-[[3-[[4-[[(4-methoxyphenyl)diphenylmethyl]amino]butyl]amino]propyl]amino]ethylidene]-5,5-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:404918 HCAPLUS
DOCUMENT NUMBER: 131:59135
TITLE: Preparation of amino acid derivatives as neuroprotective agents
INVENTOR(S): Pringle, Ashley Ker; Bradley, Mark; Sundstrom, Lars Eric; Iannotti, Fausto
PATENT ASSIGNEE(S): University of Southampton, UK
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9931049		A1	19990624	WO 1998-GB3775	19981216
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	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2315258		AA	19990624	CA 1998-2315258	19981216
AU 9915717		A1	19990705	AU 1999-15717	19981216
AU 739296		B2	20011011		
EP 1040096		A1	20001004	EP 1998-960031	19981216
EP 1040096		B1	20030709		
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NZ 505110		A	20030131	NZ 1998-505110	19981216
RU 2205177		C2	20030527	RU 2000-116112	19981216
AT 244698		E	20030715	AT 1998-960031	19981216
PT 1040096		T	20030930	PT 1998-960031	19981216
ES 2201563		T3	20040316	ES 1998-960031	19981216
CA 2355880		AA	20000622	CA 1999-2355880	19990616
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EP 1144434		A3	20020529		
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NO 2000003075		A	20000815	NO 2000-3075	20000615
HK 1029331		A1	20031003	HK 2000-108125	20001215

PRIORITY APPLN. INFO.:
GB 1997-26569 A 19971216
WO 1998-GB3775 W 19981216
WO 1999-GB1719 W 19990616

OTHER SOURCE(S): MARPAT 131:59135

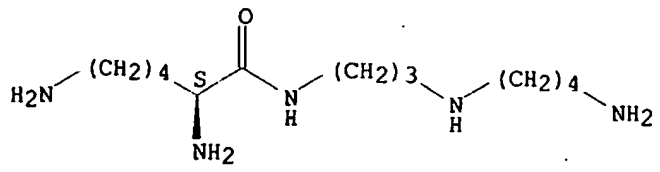
AB Amino acid derivs. Q-Ra-C*H(NR2R3)CO-Zn-NR1-Rb-NH-Rc-NH-W [Q = amidino, cyano, or amino group; Ra, Rb, Rc = (un)substituted alkylene, alkenylene; R2, R3 = H, R, RCO, RO2C, RNHCO (R = (un)substituted alkyl or aryl); the chiral atom indicated by the asterisk is in the L configuration; Z is an amino acid residue; n = 0, 1; R1 = H, (un)substituted alkyl or aryl; W = H, alkyl, aryl] were prepared as neuroprotectants. Thus, N1-L-arginylspermidine, prepared by coupling of resin-bound spermidine derivative with protected arginine, followed by deprotection/cleavage using TFA-phenol-water-triisopropylsilane-1,2-ethanedithiol, showed 99.4 % protection (relative to control hypoxia in CA1 pyramidal cell layer).

IT **134951-15-8P 191277-14-2P 191277-15-3P**
227758-27-2P 227758-28-3P 227758-29-4P
227758-31-8P 227758-32-9P 227758-33-0P
227758-34-1P 227758-35-2P 227758-36-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid derivs. as neuroprotective agents)

RN 134951-15-8 HCAPLUS

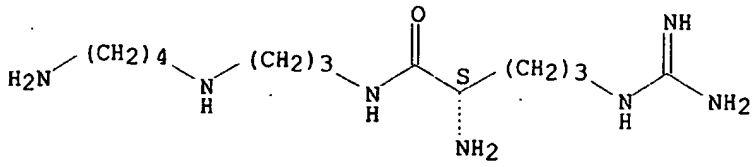
CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



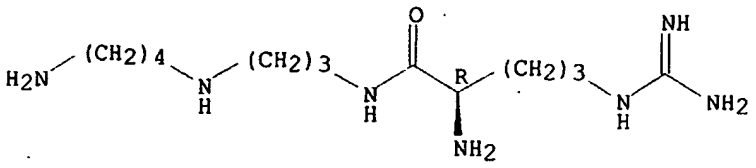
RN 191277-14-2 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



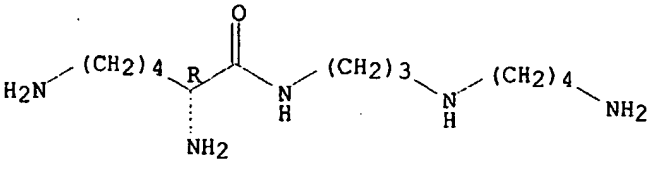
RN 191277-15-3 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



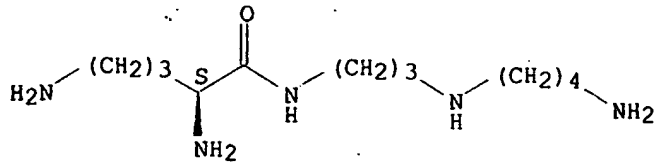
RN 227758-27-2 HCAPLUS
CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



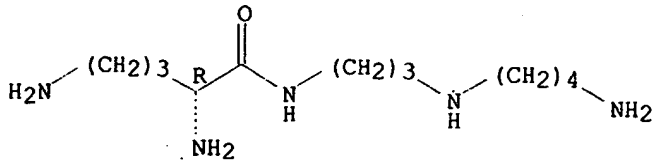
RN 227758-28-3 HCAPLUS
CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 227758-29-4 HCAPLUS
CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

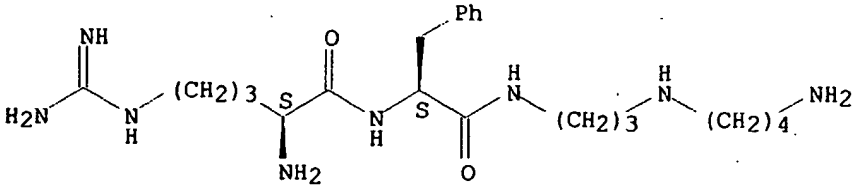


RN 227758-31-8 HCAPLUS
CN L-Phenylalaninamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-, tetrakis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

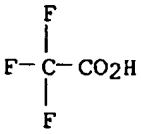
CRN 227758-30-7
CMF C22 H40 N8 O2

Absolute stereochemistry.



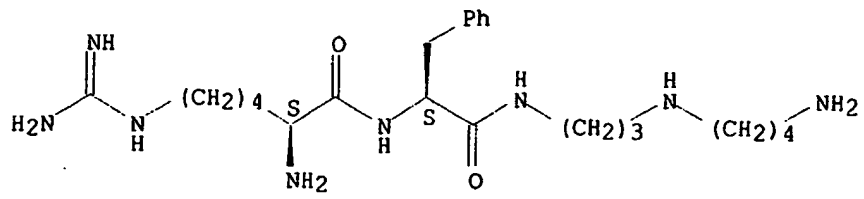
CM 2

CRN 76-05-1
CMF C2 H F3 O2



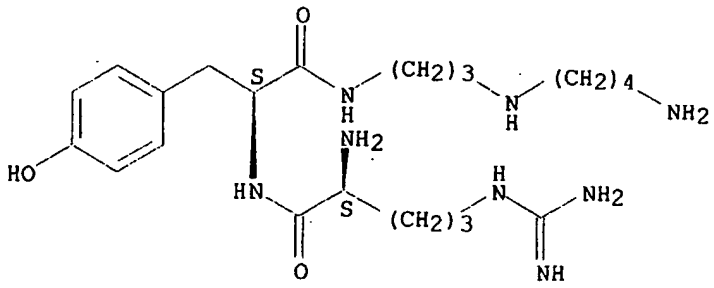
RN 227758-32-9 HCAPLUS
CN L-Phenylalaninamide, N6-(aminoiminomethyl)-L-lysyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



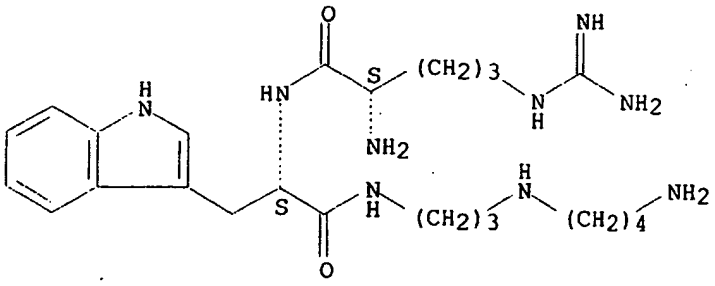
RN 227758-33-0 HCAPLUS
CN L-Tyrosinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



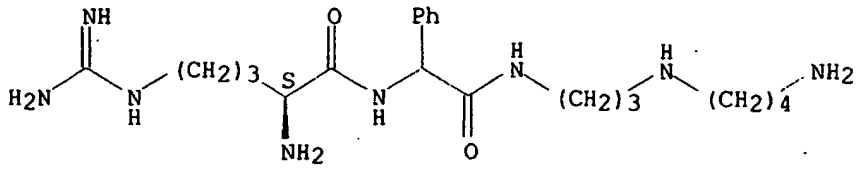
RN 227758-34-1 HCAPLUS
CN L-Tryptophanamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



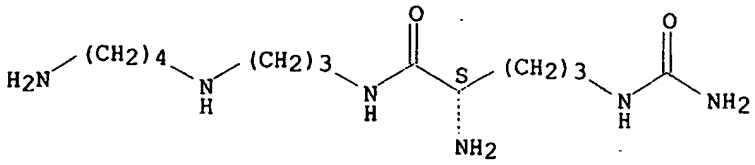
RN 227758-35-2 HCAPLUS
CN Glycinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



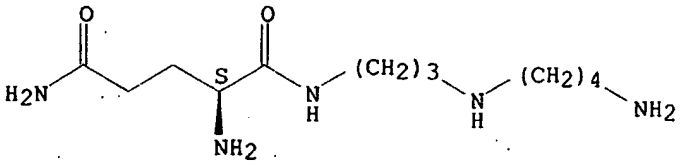
RN 227758-36-3 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



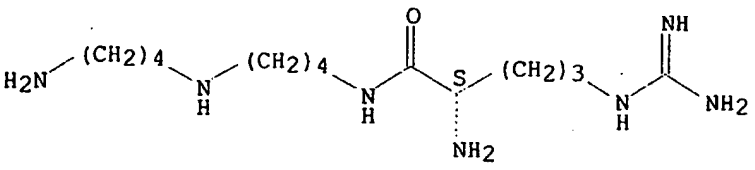
IT **227758-40-9 227758-41-0 227767-50-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid derivs. as neuroprotective agents)
RN 227758-40-9 HCAPLUS
CN Pentanediamide, 2-amino-N1-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

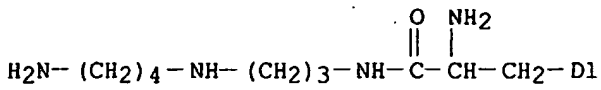


RN 227758-41-0 HCAPLUS
CN Pentanamide, 2-amino-N-[4-[(4-aminobutyl)amino]butyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

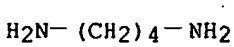
Absolute stereochemistry.



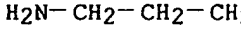
RN 227767-50-2 HCAPLUS
CN Pyridinepropanamide, α-amino-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)



IT **110-60-1**, 1,4-Butanediamine **156-87-6**
227758-37-4D, resin-bound
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of amino acid derivs. as neuroprotective agents)
RN 110-60-1 HCAPLUS
CN 1,4-Butanediamine (8CI, 9CI) (CA INDEX NAME)

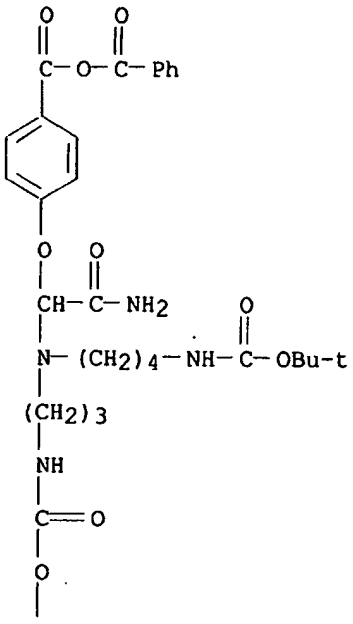


RN 156-87-6 HCAPLUS
CN 1-Propanol, 3-amino- (8CI, 9CI) (CA INDEX NAME)

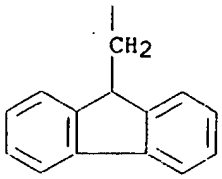


RN 227758-37-4 HCAPLUS
CN 13-Oxa-2,6,11-triazapentadecanoic acid, 6-[2-amino-1-[4-[(benzoyloxy)carbonyl]phenoxy]-2-oxoethyl]-14,14-dimethyl-12-oxo-, 9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs ind hitstr 142 1-3

L42 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:753643 HCAPLUS
DOCUMENT NUMBER: 140:280736
TITLE: Characterisation of a novel class of polyamine-based neuroprotective compounds
AUTHOR(S): **Pringle, Ashley K.**; Morrison, Barclay; **Bradley, Mark**; **Iannotti, Fausto**; **Sundstrom, Lars E.**
CORPORATE SOURCE: Clinical Neurosciences, University of Southampton, Southampton, SO16 7PX, UK
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 368(3), 216-224
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prolonged cerebral ischemia initiates complex intra- and inter-cellular signalling cascades ultimately resulting in neuronal death. Well-characterised mediators of ischemic cell death are glutamate, free radicals and nitric oxide. Many drugs that block these mechanisms are neuroprotective in vitro, but have unfavorable side-effect profiles in man. We have recently demonstrated that the compound L-arginyl-3,4-spermidine (L-Arg3,4) is neuroprotective in vitro through an interaction with several of these mechanisms, and prevents ischemic neurodegeneration in vivo with no gross side effects. In this study, we have used solid-phase combinatorial chemical, to synthesize a number of analogs of L-Arg3,4, and investigate the structure-activity relationship using an in vitro, organotypic hippocampal slice culture model of cerebral ischemia. A number of mol. features were identified which were essential for the neuroprotective activity including the requirement for a pos. charge and an amino acid in the L-configuration. Relatively minor alterations to both the terminal arginine and polyamine moieties significantly attenuated neuroprotective efficacy. Our data implies that these compds. are neuroprotective through a currently undefined mechanism rather than non-specific ionic interactions described previously for other polyamine-containing compds.

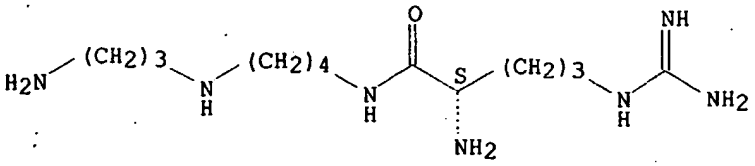
CC 1-3 (Pharmacology)
ST structure activity neuroprotectant polyamine ischemia brain hippocampus
IT Brain
(hippocampus; structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)
IT Brain, disease
(ischemia; structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)
IT Cytoprotective agents
(neuroprotective; structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)
IT Structure-activity relationship
(structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)
IT **134950-93-9 134951-15-8 141997-14-0 191277-14-2 227758-27-2 227758-28-3 227758-29-4 227758-36-3 227758-40-9 227758-41-0 675606-34-5 675606-35-6 675606-36-7 675606-37-8 675606-38-9 675606-39-0 675606-40-3**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(structure and neuroprotective activity of polyamine-based

L-arginyl-3,4-spermidine analogs)

IT **134950-93-9 134951-15-8 141997-14-0 191277-14-2 227758-27-2 227758-28-3 227758-29-4 227758-36-3 227758-40-9 227758-41-0 675606-34-5 675606-35-6 675606-36-7 675606-37-8 675606-38-9 675606-39-0 675606-40-3**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)

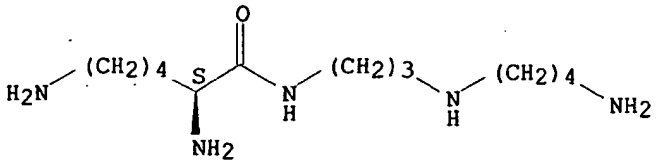
RN 134950-93-9 HCAPLUS
CN Pentanamide, 2-amino-5-[(aminoiminomethyl)amino]-N-[4-[(3-aminopropyl)amino]butyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



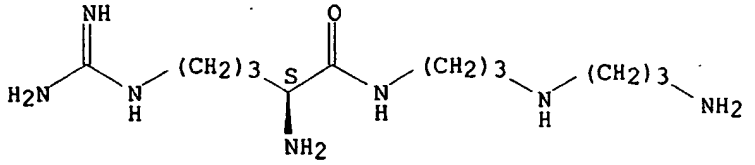
RN 134951-15-8 HCAPLUS
CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



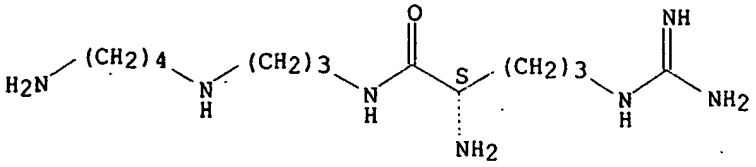
RN 141997-14-0 HCAPLUS
CN Pentanamide, 2-amino-5-[(aminoiminomethyl)amino]-N-[3-[(3-aminopropyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



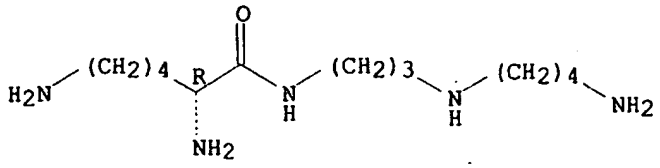
RN 191277-14-2 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



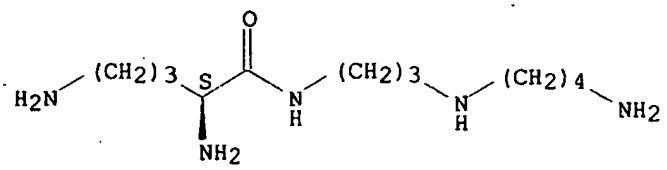
RN 227758-27-2 HCAPLUS
CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



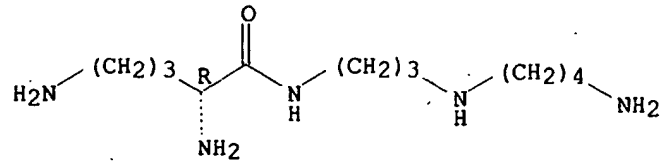
RN 227758-28-3 HCAPLUS
CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



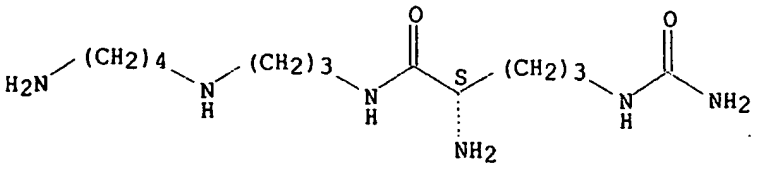
RN 227758-29-4 HCAPLUS
CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



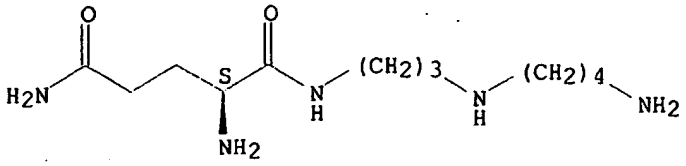
RN 227758-36-3 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



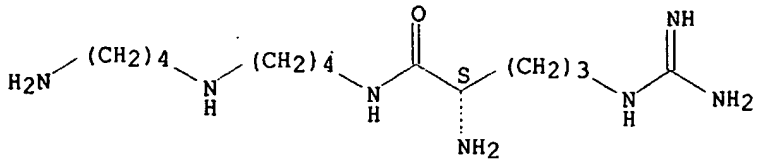
RN 227758-40-9 HCAPLUS
CN Pentanediamide, 2-amino-N1-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



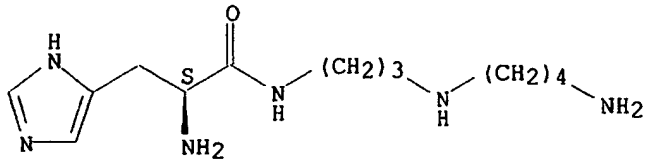
RN 227758-41-0 HCAPLUS
CN Pentanamide, 2-amino-N-[4-[(4-aminobutyl)amino]butyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



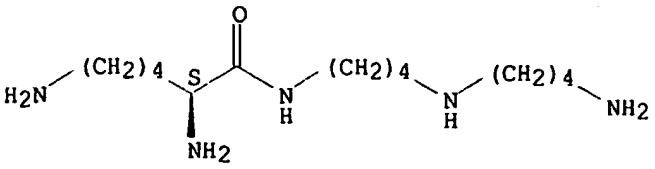
RN 675606-34-5 HCAPLUS
CN 1H-Imidazole-4-propanamide, α-amino-N-[3-[(4-aminobutyl)amino]propyl]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



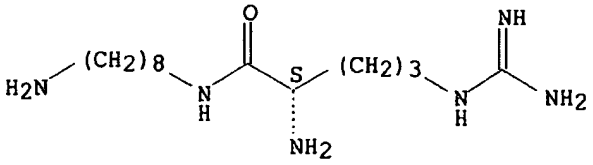
RN 675606-35-6 HCAPLUS
CN Hexanamide, 2,6-diamino-N-[4-[(4-aminobutyl)amino]butyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



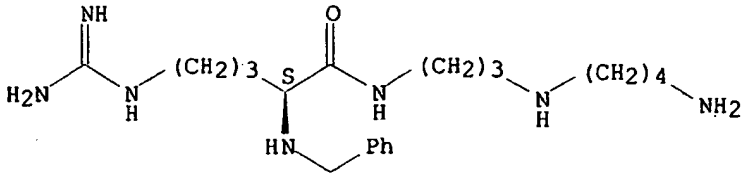
RN 675606-36-7 HCAPLUS
CN Pentanamide, 2-amino-5-[(aminoiminomethyl)amino]-N-(8-aminooctyl)-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



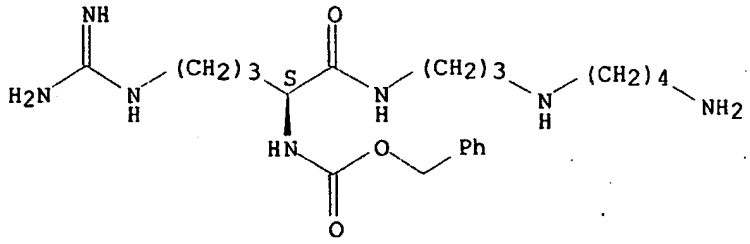
RN 675606-37-8 HCAPLUS
CN Pentanamide, N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-2-[(phenylmethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



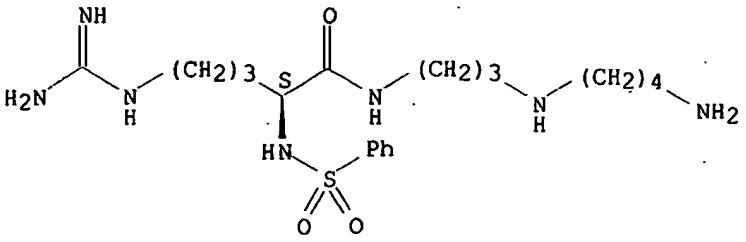
RN 675606-38-9 HCAPLUS
CN Carbamic acid, [(1S)-1-[[[3-[(4-aminobutyl)amino]propyl]amino]carbonyl]-4-[(aminoiminomethyl)amino]butyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



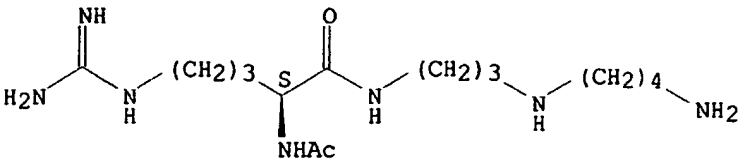
RN 675606-39-0 HCAPLUS
CN Pentanamide, N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-2-[(phenylsulfonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 675606-40-3 HCAPLUS
CN Pentanamide, 2-(acetylamino)-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:4310 HCAPLUS
DOCUMENT NUMBER: 139:30604
TITLE: L-Arginyl-3,4-spermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischaemia without suppressing synaptic transmission
AUTHOR(S): Morrison, Barclay, III; **Pringle, Ashley K.**; McManus, Terence; Ellard, John; **Bradley, Mark**; Signorelli, Francesco; **Iannotti, Fausto**; **Sundstrom, Lars E.**
CORPORATE SOURCE: Division of Clinical Neurosciences, School of Medicine, Bassett Crescent East, University of Southampton, Southampton, SO16 7PX, UK
SOURCE: British Journal of Pharmacology (2002), 137(8), 1255-1268
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1 Stroke is the third most common cause of death in the world, and there is a clear need to develop new therapeutics for the stroke victim. To address this need, we generated a combinatorial library of polyamine compds. based on sFTX-3.3 toxin from which L-Arginyl-3,4-spermidine (L-Arg-3,4) emerged as a lead neuroprotective compound In the present study, we have extended earlier results to examine the compound's neuroprotective actions in greater detail. 2 In an in vitro ischemia model, L-Arg-3,4 significantly reduced CA1 cell death when administered prior to induction of 60 min of ischemia as well as when administered immediately after ischemia. Surprisingly, L-Arg-3,4 continued to prevent cell death significantly when administration was delayed for as long as 60

min after ischemia. 3 L-Arg-3,4 significantly reduced cell death in excitotoxicity models mediated by glutamate, NMDA, AMPA, or kainate. Unlike glutamate receptor antagonists, 300 μM L-Arg-3,4 did not suppress synaptic transmission as measured by evoked responses in acute hippocampal slices. 4 L-Arg-3,4 provided significant protection, in vitro, in a superoxide mediated injury model and prevented an increase of superoxide production after AMPA or NMDA stimulation. It also decreased nitric oxide production after in vitro ischemia and NMDA stimulation, but did so without inhibiting nitric oxide synthase directly. 5 Furthermore, L-Arg-3,4 was significantly neuroprotective in an in vivo model of global forebrain ischemia, without any apparent neurol. side-effects. 6 Taken together, these results demonstrate that L-Arg-3,4 is protective in several models of neurodegeneration and may have potential as a new therapeutic compound for the treatment of stroke, trauma, and other neurodegenerative diseases.

CC 1-11 (Pharmacology)

ST arginylspermidine neuroprotective forebrain ischemia stroke

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA-binding; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Brain, disease
(forebrain, ischemia; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Brain
(hippocampus, sector CA1, cell death inhibition; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Cytoprotective agents
(neuroprotective; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Toxicity
(neurotoxicity, excitotoxicity; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Brain, disease
(stroke; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Neurotransmission
(synaptic; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Nerve
(toxicity, excitotoxicity; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT **56-86-0**, L-Glutamic acid, biological studies **487-79-6**, Kainic acid **6384-92-5** **10102-43-9**, Nitric oxide, biological studies **11062-77-4**, Superoxide
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

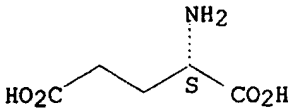
IT **191277-14-2**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT **56-86-0**, L-Glutamic acid, biological studies **487-79-6**, Kainic acid **6384-92-5** **10102-43-9**, Nitric oxide, biological studies **11062-77-4**, Superoxide
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

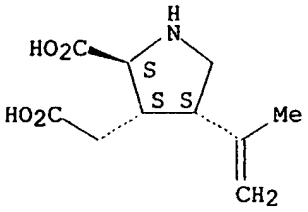
RN 56-86-0 HCAPLUS
CN L-Glutamic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.



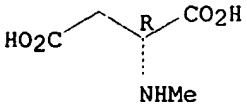
RN 487-79-6 HCAPLUS
CN 3-Pyrrolidineacetic acid, 2-carboxy-4-(1-methylethenyl)-, (2S,3S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 6384-92-5 HCAPLUS
CN D-Aspartic acid, N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



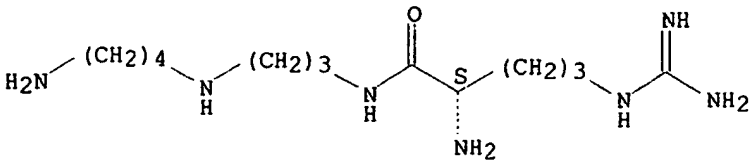
RN 10102-43-9 HCAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

RN 11062-77-4 HCAPLUS
CN Superoxide (8CI, 9CI) (CA INDEX NAME)

O=O

IT **191277-14-2**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)
RN 191277-14-2 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:404918 HCAPLUS
DOCUMENT NUMBER: 131:59135
TITLE: Preparation of amino acid derivatives as neuroprotective agents
INVENTOR(S): **Pringle, Ashley Ker; Bradley, Mark ; Sundstrom, Lars Eric; Iannotti, Fausto**
PATENT ASSIGNEE(S): University of Southampton, UK
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9931049	A1	19990624	WO 1998-GB3775	19981216
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315258	AA	19990624	CA 1998-2315258	19981216
AU 9915717	A1	19990705	AU 1999-15717	19981216
AU 739296	B2	20011011		
EP 1040096	A1	20001004	EP 1998-960031	19981216
EP 1040096	B1	20030709		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2002508349	T2	20020319	JP 2000-538979	19981216
NZ 505110	A	20030131	NZ 1998-505110	19981216
RU 2205177	C2	20030527	RU 2000-116112	19981216
AT 244698	E	20030715	AT 1998-960031	19981216
PT 1040096	T	20030930	PT 1998-960031	19981216
ES 2201563	T3	20040316	ES 1998-960031	19981216
CA 2355880	AA	20000622	CA 1999-2355880	19990616
WO 2000035941	A2	20000622	WO 1999-GB1719	19990616
WO 2000035941	A3	20011004		

W: CA, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

EP 1144434	A2	20011017	EP 1999-936759	19990616
EP 1144434	A3	20020529		

R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE

NO 2000003075	A	20000815	NO 2000-3075	20000615
HK 1029331	A1	20031003	HK 2000-108125	20001215

PRIORITY APPLN. INFO.: GB 1997-26569 A 19971216
WO 1998-GB3775 W 19981216
WO 1999-GB1719 W 19990616

OTHER SOURCE(S): MARPAT 131:59135

AB Amino acid derivs. Q-Ra-C*H(NR2R3)CO-Zn-NR1-Rb-NH-Rc-NH-W [Q = amidino, cyano, or amino group; Ra, Rb, Rc = (un)substituted alkylene, alkenylene; R2, R3 = H, R, RCO, RO2C, RNHCO (R = (un)substituted alkyl or aryl); the chiral atom indicated by the asterisk is in the L configuration; Z is an amino acid residue; n = 0, 1; R1 = H, (un)substituted alkyl or aryl; W = H, alkyl, aryl] were prepared as neuroprotectants. Thus, N1-L-arginylspermidine, prepared by coupling of resin-bound spermidine derivative with protected arginine, followed by deprotection/cleavage using TFA-phenol-water-triisopropylsilane-1,2-ethanedithiol, showed 99.4 % protection (relative to control hypoxia in CA1 pyramidal cell layer).

IC ICM C07C237-10
ICS C07C257-14; A61K031-155; A61K031-16

CC 34-2 (Amino Acids, Peptides, and Proteins)

ST arginylspermidine prepn neuroprotectant; spermidine arginyl prepn neuroprotectant

IT Structure-activity relationship
(neuroprotectant; preparation of amino acid derivs. as neuroprotective agents)

IT Cytoprotective agents
(neuroprotectants; preparation of amino acid derivs. as neuroprotective agents)

IT Ischemia
(preparation of amino acid derivs. as neuroprotective agents)

IT Amino acids, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid derivs. as neuroprotective agents)

IT **134951-15-8P 191277-14-2P 191277-15-3P**
227758-27-2P 227758-28-3P 227758-29-4P
227758-31-8P 227758-32-9P 227758-33-0P
227758-34-1P 227758-35-2P 227758-36-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid derivs. as neuroprotective agents)

IT **227758-40-9 227758-41-0 227767-50-2**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid derivs. as neuroprotective agents)

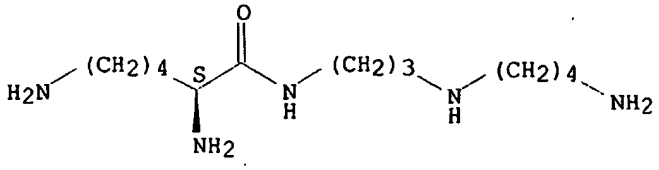
IT **110-60-1**, 1,4-Butanediamine **156-87-6**
227758-37-4D, resin-bound
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of amino acid derivs. as neuroprotective agents)

IT **227758-39-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amino acid derivs. as neuroprotective agents)

IT **134951-15-8P 191277-14-2P 191277-15-3P**
227758-27-2P 227758-28-3P 227758-29-4P
227758-31-8P 227758-32-9P 227758-33-0P
227758-34-1P 227758-35-2P 227758-36-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid derivs. as neuroprotective agents)

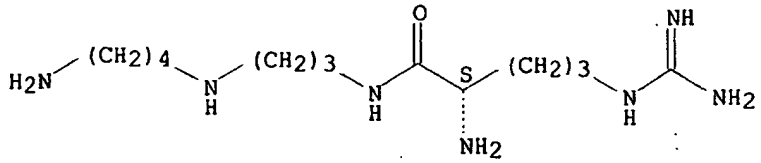
RN 134951-15-8 HCAPLUS
CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



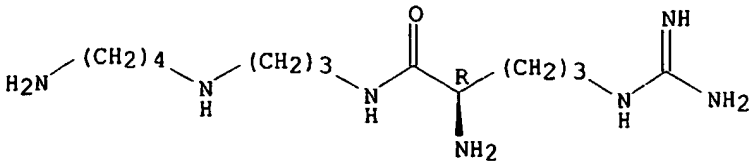
RN 191277-14-2 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



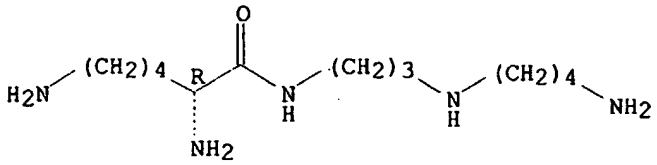
RN 191277-15-3 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



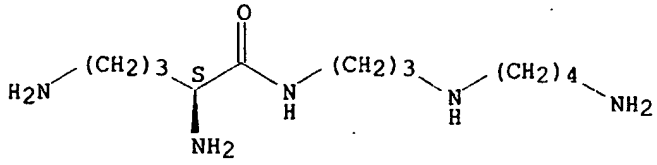
RN 227758-27-2 HCAPLUS
CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



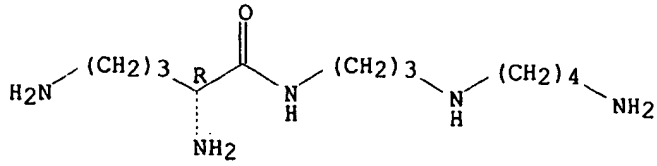
RN 227758-28-3 HCAPLUS
CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 227758-29-4 HCAPLUS
CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

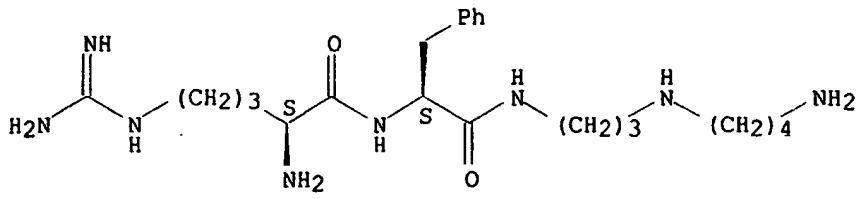


RN 227758-31-8 HCAPLUS
CN L-Phenylalaninamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-, tetrakis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

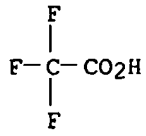
CRN 227758-30-7
CMF C22 H40 N8 O2

Absolute stereochemistry.



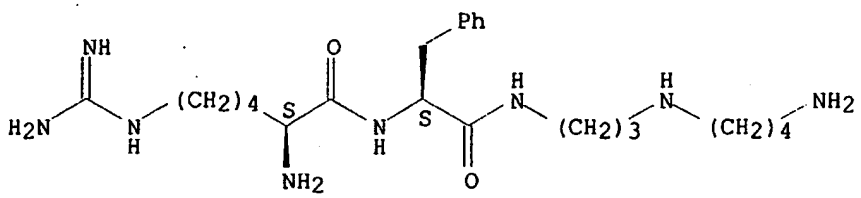
CM 2

CRN 76-05-1
CMF C2 H F3 O2



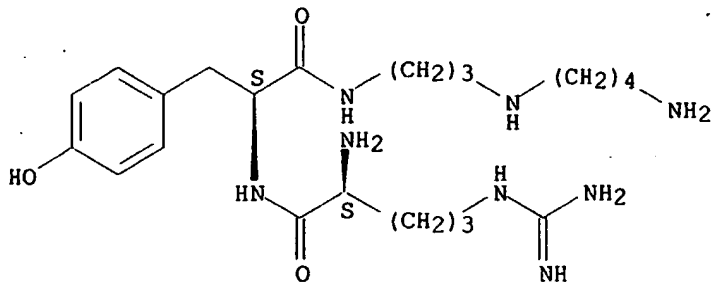
RN 227758-32-9 HCAPLUS
CN L-Phenylalaninamide, N6-(aminoiminomethyl)-L-lysyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 227758-33-0 HCAPLUS
CN L-Tyrosinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

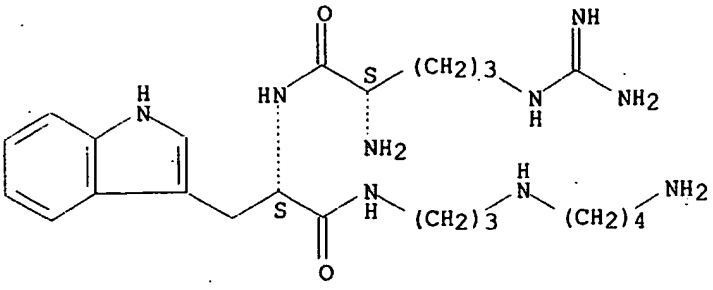
Absolute stereochemistry.



RN 227758-34-1 HCAPLUS

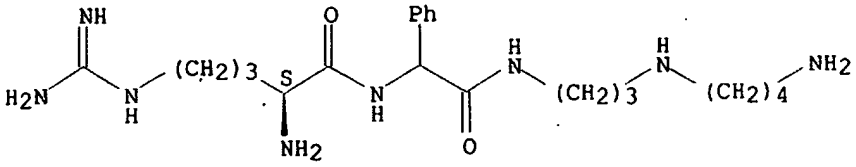
CN L-Tryptophanamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



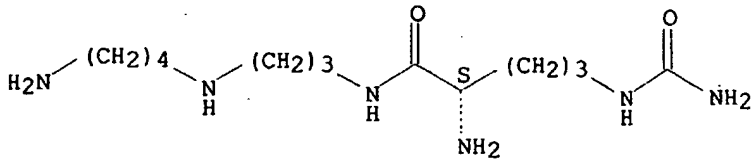
RN 227758-35-2 HCAPLUS
CN Glycinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



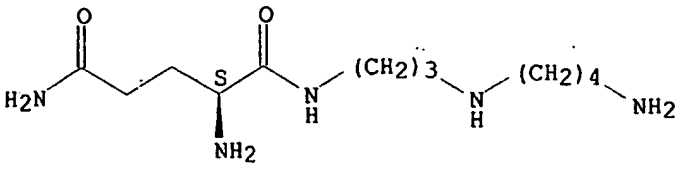
RN 227758-36-3 HCAPLUS
CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



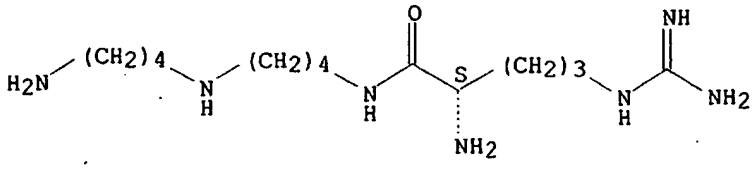
IT **227758-40-9 227758-41-0 227767-50-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid derivs. as neuroprotective agents)
RN 227758-40-9 HCAPLUS
CN Pentanediamide, 2-amino-N1-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

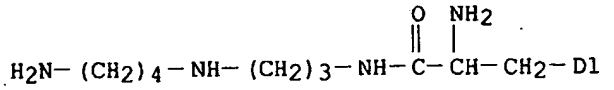


RN 227758-41-0 HCAPLUS
CN Pentanamide, 2-amino-N-[4-[(4-aminobutyl)amino]butyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

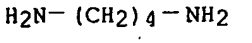


RN 227767-50-2 HCAPLUS
CN Pyridinepropanamide, α-amino-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

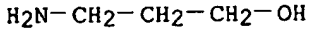


IT **110-60-1**, 1,4-Butanediamine **156-87-6**
227758-37-4D, resin-bound
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of amino acid derivs. as neuroprotective agents)

RN 110-60-1 HCAPLUS
CN 1,4-Butanediamine (8CI, 9CI) (CA INDEX NAME)



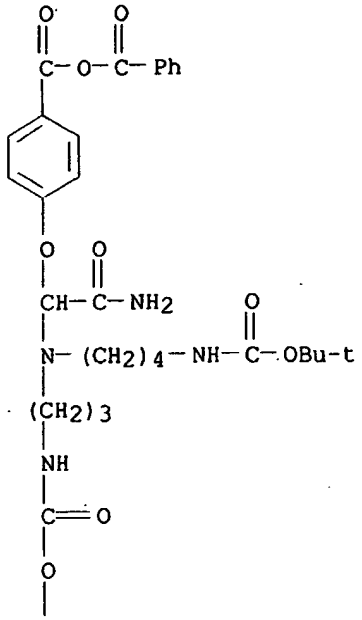
RN 156-87-6 HCAPLUS
CN 1-Propanol, 3-amino- (8CI, 9CI) (CA INDEX NAME)



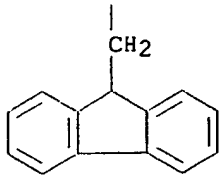
RN 227758-37-4 HCAPLUS
CN 13-Oxa-2,6,11-triazapentadecanoic acid, 6-[2-amino-1-[4-[(benzoyloxy)carbonyl]phenoxy]-2-oxoethyl]-14,14-dimethyl-12-oxo-,

9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

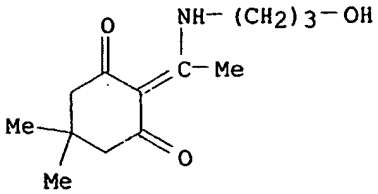
PAGE 1-A



PAGE 2-A



IT **227758-39-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amino acid derivs. as neuroprotective agents)
RN 227758-39-6 HCAPLUS
CN 1,3-Cyclohexanedione, 2-[1-[(3-hydroxypropyl)amino]ethylidene]-5,5-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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